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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,498	01/30/2002	Jong-Gu Park	57354-00002	5213

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,498	PARK ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-39,46,47,50-59,62 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-39,46,47,50-59,62 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 13 July 2006 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 13 July 2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 13 July 2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 30-39, 46, 47 50-59, 62, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellmann et al., in view of Moon et al., LaPlante et al., Hu et al., and Gewirtz *et al.* (all of record), and is repeated for the same reasons of record as set forth 22 April 2005.

Applicants have traversed the instant rejection by asserting that while Hellmann indeed teaches a large circular single-stranded nucleic acid molecule comprising at least one target

specific antisense region that is effective for reducing expression of said gene, Hellmann lacks the transfection reagents as claimed instantly. Since Hellmann teaches large circular vector-based antisense inhibition of target expression, one of ordinary skill in the antisense art would understand that it is obvious to combine such compounds with transfection agents such as those claimed instantly. This is evidenced by the secondary references of Moon, LaPlante, and Hu, all of whom teach transfection of circular nucleic acids relating to antisense inhibitors into cells using transfection reagents. Thus while Hellmann may not teach a transfection reagent, Hellmann was not relied upon for this. It is the references of Moon, LaPlante, and Hu that directly teach that transfection agents are commonly used in compositions comprising antisense inhibitors. Since Hellmann teaches antisense inhibition, Applicants' assertions that Hellmann's cell free system is not combinable with teachings of circular antisense inhibition in cells are not convincing because one of ordinary skill in the antisense art would understand that Hellmann does not teach away from the use of such inhibitors, and because one of skill in the antisense art would have viewed the large circular single-stranded antisense nucleic acids of Hellmann in view of Moon, LaPlante, and Hu as suggesting the use of large circular nucleic acids, and would have known that the use of such transfection agents with such compounds are commonly adopted.

Applicants argue that each of Moon, LaPlante, and Hu separately fail to disclose or suggest the presently claimed inventive composition. However, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re*

Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue that Hellmann is not combinable with Moon, LaPlante, Hu, or Gewirtz, because Hellmann discloses only a cell free system, which according to Applicants, presents a separate and unique challenge from the systems of Moon LaPlante and Hu, which are cell based. Applicants conclude that the Hellmann and Moon references are thus not analogous art and are not combinable. This basis for asserting that Hellmann and Moon are not analogous art is not convincing, because both Hellmann and Moon use large circular antisense-containing nucleic acids to inhibit gene expression, and therefore, not only are they considered analogous, they are also considered to have significant literal overlap in their teachings. In fact, the only areas of non-overlap are that the circular antisense of Moon et al. are smaller, and utilize liposomes to facilitate cellular entry. Although Hellmann's method is taught in a cell free system, which contrasts with the cell based system of Moon, the fact that both use large circular nucleic acids comprising antisense regions to inhibit the expression of a specific target gene would suggest to one of ordinary skill in the antisense art that these references are indeed combinable.

Although Moon teaches the use of cationic liposomes to enhance the cellular uptake of relatively large single-stranded circular nucleic acids comprising in antisense region, applicants argue that Moon alone does not suggest that successful transfection can take place with a large circular single-stranded nucleic acid that is at least 3000 bases long, because the oligos of Moon are only 116 nucleotides long. Even if this point were to be granted, which it is not, this argument ignores the fact that LaPlante and Hu both teach transfection of large plasmids that are at least about 3000 nucleotides long using transfection agents identical to that claimed instantly,

for the purpose of antisense mediated target inhibition. Furthermore, the assertion that Moon fails to suggest that transfection of large nucleic acids at least about 3000 nucleotides long would be successful is contradicted by the statement by the statement in Moon at page 4652, "from the experience of our own and other groups, a meaningful level of AS all ago uptake should be consistently attainable when carried into cells by liposomes, *regardless of the size of AS oligos* (31, 32)." (Emphasis added).

The LaPlante disclosure is asserted by applicants to fail to provide any motivation to transfect a large circular single-stranded nucleic acid molecule. However, LaPlante discloses transfection of a target specific antisense cDNA. This is the feature for which LaPlante is relied upon. The fact that LaPlante doesn't teach said antisense as a circular nucleic acid was *not* a feature for which LaPlante was relied upon. The limitation of "circular" is taught by Moon, as well as Hellmann, both of which also teach antisense mediated inhibition. Therefore, Applicants' arguments that Hellmann and LaPlante are not analogous is not convincing, merely because Hellmann uses a cell free assay whereas LaPlante utilizes a cell based assay. Both references utilize large antisense nucleic acids for target specific inhibition.

Applicants also assert that Hellmann fails to be combinable with Hu, because Hu's research field is focused on inhibiting target gene expression by the expression of exogenously introduced plasmid DNA that expresses antisense RNA. Applicants reiterate their belief that Hellmann's cell free system renders it non-combinable with a reference such as that of Hu, which teaches cellular antisense-mediated inhibition. Applicants state that "a person in the art of target gene inhibition by expression of antisense RNA would not look to a cell free assay system for guidance in solving its problems."

However, demonstration of a prima facie case of obviousness does not require a reference to go in search of guidance to solve problems. It's not clear to the examiner what "problems" would need to be solved. The question is whether or not there is sufficient motivation to combine the large circular antisense-containing nucleic acid of Hellmann et al. with a lipid component as taught by Moon et al., LaPlante et al., Hu et al., or Gewirtz et al. It is set forth that A) Hellmann successfully inhibits gene expression in a cell free system, and B) this would be recognized by one of ordinary skill in the antisense art as a reason to combine said nucleic acid with a lipid component to inhibit gene expression in a cell. The overlap is significant between Hellmann in the other references, because as stated above, and as evidenced by Moon, LaPlante, and Hu, those of ordinary skill in the antisense art understand that it is common to use transfection agents in antisense mediated gene inhibition.

Finally, applicants argue that Gewirtz is not combinable with the Hellmann reference because Gewirtz is concerned with better efficiency of oligos and does not mention large circular stranded nucleic acids. However, Gewirtz was not relied upon for he teaching of large circular stranded nucleic acids, but for he teaching that antisense oligos are commonly utilized with transfection agents, a fact apparently conceded by applicants statement that at page 17 of their arguments: "transfection effective agents for nucleic acids were known in the art at the time of the invention as exemplified by Gewirtz". The reference of Gewirtz was cited to provide evidence that antisense nucleic acids with demonstrated inhibitory capacity, such as that taught by Hellmann, are commonly mixed with transfection agents, such as those claimed instantly by applicants.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Applicants have conceded in their arguments on page 17 that each of the separate ingredients were in existence at the time of applicants filing. Applicants have not argued that Hellmann demonstrates antisense mediated target specific inhibition. As is made clear by Moon, LaPlante, and Hu, one of ordinary skill in the antisense art would understand that transfection effective agents are commonly used with antisense nucleic acids.

Applicants have asserted that the cited references fall short of the motivation for combining "because none of the cited references recognizes or appreciates that the effective usefulness of transfecting these large circular single-stranded nucleic acid molecules into eukaryotic cells." (Applicants arguments page 17). However, applicants claimed invention is not a method but a composition. Hellman teaches the use of a large, circular, single-stranded nucleic acid molecule comprising an antisense region to inhibit gene expression. While the experiments were done in a cellular homogenate, this does not mitigate the fact that the composition of Hellmann teaches all of the instantly claimed elements except for the transfection effective agent. Moon teaches the use of circular single-stranded nucleic acid molecules comprising an antisense region to inhibit gene expression *in cells*. LaPlante and Hu both teach transfection of antisense sequences into cells for the purpose of achieving gene specific inhibition of expression using

transfection effective carriers. Gewirtz teaches that antisense mediated inhibition in cells is commonly achieved using transfection effective carriers.

Applicants have also argued that Hellmann shows the opposite of the inventive concept because Hellmann shows a large circular single-stranded nucleic acid molecule that is used in the cell free system. It is not clear how Hellmann can teach the opposite of applicants invention, when Hellmann teaches everything except the transfection mediating liposome. The fact that Hellmann teaches gene inhibition using large circular single-stranded antisense-containing nucleic acids would suggest to a researcher in the antisense arts to use such molecules in cells since this is where antisense inhibition would have its most relevant and biologically interesting results. Applicants have stated that it must be appreciated that applicants are the first to transfect these large circular single-stranded nucleic acids into cells to achieve antisense inhibition. However, Hellmann et al. uses large circular single-stranded nucleic acids to achieve gene inhibition, Moon et al. uses small circular single-stranded nucleic acids to achieve gene inhibition in cells, LaPlante et al. uses large circular plasmids to transfect large antisense expressing plasmids into cells to achieve antisense-mediated inhibition.

Applicants have argued that there was no suggestion in the prior art that a large circular single-stranded nucleic acid was desirable for transfection into eukaryotic cell to achieve any purpose at all. Again, Hellmann et al. teaches gene inhibition. Gene inhibition is a desirable result, particularly to anyone interested in research or therapeutics. The idea that gene inhibition would only be desirable in a cell free system is simply not adopted. Similarly, the idea that gene inhibition in a cell free system is not analogous to gene inhibition in a cell is also not adopted.

Applicants argue from Gewirtz that they were essentially two types of antisense strategies at the time of the invention, ribozymes and antisense oligonucleotides. Of course, this argument completely ignores the contribution of Hellmann et al. who teaches an antisense strategy comprising every aspect of applicants instantly claimed invention minus a transfection agent. Applicants argue that the large circular single-stranded nucleic acids of the instant invention cannot be grouped with the large double stranded antisense expressing molecule. Applicants have provided no evidence or reasoning beyond a very generalized statement that "the biochemical characterization of a single-stranded and double stranded molecule revealed different results." The double stranded molecule cited is very large, and has been successfully shown to be transfected into cells whereupon a large antisense molecule is transcribed which inhibits its target. Applicants generalized statement does not overcome this very specific teaching. Applicants also object to any reliance upon prior art which teaches oligonucleotides since oligonucleotides are short in the instantly claimed composition has over 3000 bases. However, the successful use of large antisense expressing plasmids, which are actually larger than applicants instantly claimed compositions, undercut applicants assertion that "just based on sheer difference in size," that there would be no apparent expectation of success. Accordingly, applicants generalized statement in the absence of any other evidence or reasoning is not considered overcome such specific teachings of the prior art.

Finally, applicants point to a recently published article in Nature Biotechnology by the applicants, among others, which is alleged by applicants to support the notion that the instantly claimed invention is acknowledged in scientific circles to be of significant advance over existing knowledge antisense technology. While it is acknowledged that such a publication is evidence

that the instant invention works in cells, it does not expand upon what has already taught in the instant specification and as already been considered by the examiner. It is reiterated that the instant claims are drawn to a composition which is largely taught in the prior art by Hellmann et al. The only factor missing in Hellmann et al. is a transfection agent, which is very well-known in the prior art, which makes the instant invention almost an anticipation type situation. Quite simply, there is no evidence in the cited prior art that would suggest that applicants claimed invention would not work in cells. And since Hellmann teaches gene inhibition, a process which one of ordinary skill in the art would understand to have great value when accomplished in a cell, there is considered to be substantial motivation to transfect the constructs of Hellmann into cells. The rejection is maintained therefore.

No claims are allowed.

Conclusion

This is an RCE of Application No. 10/066,498. All claims are drawn to the same invention claimed earlier and that were finally rejected on the grounds and art of record. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JDS

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